Reactions of Some 1-Arylpiperazines and 1-Aryl-4-(2-Hydroxy-3-Methoxypropyl) Piperazines

By

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CHAPTER I

INTRODUCTION

For thousands of years, man has separated materials from his natural environment and used them to alter the chemical or physical processes within his body. In general, these substances, known today as drugs or medicinal agents, may be said to have been used for their curative and protective powers against harmful substances within the body, for the elimination of parasitic organisms of both visible and microscopic sizes, or for the production of a desired level of sedation, anesthesia or hypnosis.

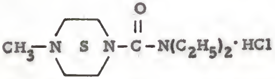
The use of organic materials for this purpose dates from the earliest history of medicine. The source of such drugs[1,2,3] was originally the extracts of certain familiar plants. For example, a Chinese herbal of the fifth century, B.C., describes the hemp plant whose flowering top provided cannabis (marihuana), which the Chinese used as an anesthetic in surgery two thousand years ago. An authentic reference was made in the third century, B.C., by Theophrastus to the juice of the poppy capsules from which opium is extracted. The antipyretic property of willow bark, from which salicin was later isolated, was known to the ancients. Colchicine, found in the seeds of the autumn crocus of Asia Minor, was recommended in the sixth century, A.D., for pain of articular origin. The powdered leaf of the foxglove was a source of digitalis and the leaves of a certain tree from the mountains of Peru and Bolivia still provide one of the sources of cocaine. The early European explorers of Brazil found ipecac ("Brazil root") used as an emetic agent. The root was later shown to contain the active agent emetine. The products of such plants as those yielding coffee, tea and cocoa are still used all over the world to provide beverages which contain caffeine or theobromine.

The use of synthetic organic materials as therapeutic agents can probably be dated from the nineteenth century with the introduction of ether and chloroform as anesthetics. The knowledge of the chemistry of certain natural products acquired in the early development of the science quickly led to the use of other related natural substances, and subsequently to the isolation and synthesis of the active components of these products. This can be illustrated by the use of both willow and cinchona bark for antipyretic purposes and finally the isolation and characterization of salicyl alcohol glucoside and the preparation of the related compound, acetylsalicylic acid.

This approach has led to a variety of researches which have resulted in the discovery and introduction of new therapeutic materials. Some drugs, such as phenacetin, are developed as the result of observations of biological processes. Occasionally, as in the case of penicillin and of dramamine, discoveries are made accidentally by perceptive persons in the course of other work. Other compounds are examined because of their chemical relationship to active congeners. Sometimes, because compounds containing specific structural units have been shown to have certain desired physiological effects, compounds are synthesized with a specific purpose in mind. A few drugs such as quinacrine (Atabrine), chloroquine (Aralen) and chlorguanide (Paludrine) have come only from laborious screening processes having as their objectives the discovery of compounds which satisfy a definite need.

The purpose of the present research was to prepare several series of derivatives of piperazine with molecular structures containing arrangements of functional groups known to have pharmalogical activity as anthelmintic, antihistiminic and tranquilizing agents.

The anthelmintic properties of piperazine and its effectiveness against such parasites as ascarids and various oxyuridae is well known. The high level of filarial infestation of American military personnel while stationed in the western Pacific during World War II stimulated the research which resulted in the preparation of the highly effective diethylcarbamazine hydrochloride (hetrazane) by Kushner, et al.[4]

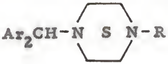


diethylcarbamazine hydrochloride

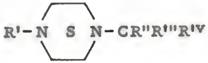
The aminoethers, particularly those of the ethanol amine series, have been used successfully as antihistimines. Compounds having the general structure,

$$R-O-CH_2CH_2NR'R'',$$

have been found to be especially effective antihistimines when R is the benzhydryl group.[5,6] Other active compounds are the benzhydryl, or substituted benzhydryl, derivatives of monosubstituted piperazines.[7-15]



Later work[16] has included such structural arrangements as

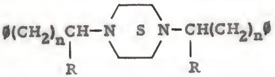


R' = Carboxyalkyl

R" = H or shortchain alkyl

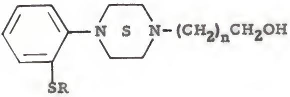
R'''R'V = groups which may, or may not,
be aromatic

In recent years, especially since 1957, there has been a widespread interest in similarly disubstituted piperazines with respect to their effect on the central nervous system. Symmetrically substituted piperazines of the type

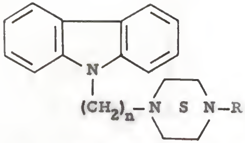


$n = 0$ to 10 $\qquad$ $R = 1$ to 8 C atom alkyl

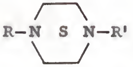
as well as their salts have been found to have therapeutic use as medullary depressants, narcosis potentiators, and dilators of cortical vessels.[17] Derivatives of the following forms have been prepared for their properties in the treatment of hypertension and anxiety states:[18-20]



$R = CH_3, C_2H_5$ $\qquad$ $n = 2$ to 5



$R = H, CH_3, C_2H_5, n\text{-}C_3H_7 \qquad n = 2, 3$

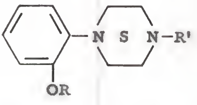


$R =$ substituted benzhydryl

$R' = CH_2CH_2OCH_2CH_2OH$ or

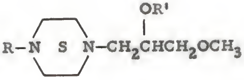
$CH_2CH_2OCH_2CH_2OCH_2CH_2OH$

A series of substituted phenylpiperazines[21] which have been effective against progressive hypertension and hypertensive encephalopathy and which closely approximate the general structure of some of the compounds prepared in the course of this research have the following formula.

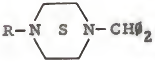


$R = CH_3, C_2H_5 \qquad R' = (CH_2)_3OCH_3, (CH_2)_2OCH_3$

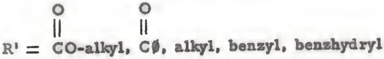
The compounds prepared in the present research corresponded to the following general formulas:



and



R = phenyl or substituted phenyl



$R' = \overset{O}{\overset{\|}{C}}\text{O-alkyl}, \overset{O}{\overset{\|}{C}}\text{Ø}$, alkyl, benzyl, benzhydryl

All of these compounds are new and will be submitted to Parke, Davis and Company for testing.

CHAPTER II

EXPERIMENTAL

All yields reported in this chapter are based on the reactant present in the least stoichiometric quantity. All temperatures refer to the centigrade scale and its symbol is omitted. Melting points are uncorrected.

The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Source of Starting Materials

Several of the substituted piperazines used in this research were unavailable from commercial sources and consequently were prepared in this laboratory. The method of Pollard, *et al.*,[22,23] was used for the preparation of the N-phenylpiperazines bearing the following substituents on the phenyl group: 2-methyl-, 3-methyl-, 4-methyl-, 2-chloro-, 3-chloro-, and 4-chloro-. Those bearing the substituents 4-ethoxy-, 2-methyl-3-chloro-, 2-methyl-5-chloro-, 2-chloro-5-methyl-, 3-chloro-4-methyl- were prepared according to Prelog, *et al.*,[24,25] as modified by Parcell.[26]

N-(2-Methoxyphenyl)piperazine, N-(2-ethoxyphenyl)-piperazine, N-(2-ethylphenyl)piperazine, and N-(2-propylthiophenyl)-piperazine were furnished as research samples by Parke, Davis and Company.

The starting materials listed below were obtained from the commercial sources indicated and, unless otherwise stated in the text, were used without further purification.

1,2-Epoxy-3-methoxypropane	Peninsular ChemResearch, Inc.
Benzhydryl bromide	Aldrich Chemical Company
Benhydryl chloride	Eastman Kodak Company
N-Phenylpiperazine	Chemopuro Manufacturing Corporation
Sodium hydride (54% suspension in mineral oil)	Metal Hydrides, Inc.

1-Chloro-2-hydroxy-3-methoxypropane was prepared by an adaptation of the method of Fairbourne, et al.,[27] for the preparation of 1-chloro-2-hydroxy-3-ethoxypropane. Concentrated sulfuric acid (20 ml.) was added to methanol (1615 ml.) and epichlorohydrin (314 ml.) was then added dropwise with stirring. The solution was refluxed overnight, cooled, and neutralized to a phenolphthalin endpoint with concentrated, aqueous sodium hydroxide. The solvent was removed by passing the solution through a steam-heated coil under vacuum from a water aspirator and the residue was distilled at 20 mm. pressure. The product was collected between 80° and 85°.

1-Phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine was prepared, with slight modifications, by the method of Pollard and Wicker.[28] The modifications consisted of heating a mechanically-stirred mixture of the reactants at 90° to 100° instead of heating with occasional agitation on the steam bath and of extraction and recrystallization of the product with ether instead of heptane. These modifications resulted in increased yields of purified product and eliminated the necessity for handling the comparatively large volume of heptane which was required for solution of the product.

The benzene and toluene used in the preparation of the sodium alcoholate intermediates were purified by treatment with concentrated sulfuric acid according to Fieser.[29] The solvent was then filtered through absorbent cotton and distilled to a trap for removal of remaining water. The dried residue was distilled at atmospheric pressure.

Reactions of 1-Arylpiperazines with Benzhydryl Chloride

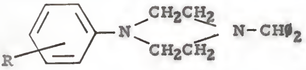
Eleven 1-arylpiperazines were reacted with equimolar amounts of benzhydryl chloride in the presence of sodium carbonate to give the corresponding 1-aryl-4-benzhydryl piperazines. All eleven derivatives were prepared by the same general method described below. The physical and analytical data for the products are listed in Table 1.

Preparation of 1-aryl-4-benzhydryl piperazine

Sodium carbonate (0.2M) was placed with N-substituted piperazine and benzene (100-150 ml.) in a 300 ml., round-bottom flask containing a magnetic stirring bar and equipped with a condenser and trap for removing water. The mixture was refluxed with stirring until any water present had been eliminated. The trap was then removed and while the mixture was still hot, benzhydryl chloride (0.1M) was added. After this mixture had refluxed for at least three hours, it was filtered and hexane washings of the solid material added to the filtrate. The solids were dissolved in a minimum amount of water or aqueous sodium hydroxide and extracted several times with ether. The residue, if any, from evaporation of the ether extracts was added to the benzene-hexane filtrate and the solution evaporated on the steam bath. If the residue was acid, it was treated with aqueous sodium hydroxide and extracted several times with hexane. The combined hexane extracts were evaporated on the steam bath almost to dryness. The crystalline material obtained during the evaporation was removed by filtration and recrystallized from hexane or 95 percent ethanol.

TABLE 1

1-ARYL-4-BENZHYDRYL PIPERAZINES



					Analyses	
R	Percent Yield	Recrystallizing Solvent	Melting Point	% C Calcd. Found	% H Calcd. Found	% N Calcd. Found
2-CH_3-	37	hexane	119 -120	84.17 84.12	7.65 7.72	8.18 8.35
3-CH_3-	10	hexane	90.5- 91.5	84.17 84.02	7.65 7.75	8.18 8.27
4-CH_3-	32	heptane	133 -133.5	84.17 83.99	7.65 7.63	8.18 8.06
2-Cl-	41	ethanol	94.5- 95.5	76.12 76.34	6.39 6.60	7.72 7.45
3-Cl-	19	hexane	108 -109	76.12 76.25	6.39 6.26	7.72 7.70
4-Cl-	23	hexane	130 -131	76.12 76.31	6.39 6.41	7.72 7.72
2-CH_3O-	28	ethanol	116 -117	80.41 80.35	7.31 7.46	7.82 7.86
2-CH_3- 3-Cl-	33	ethanol	120 -121	76.47 76.57	6.69 6.70	7.43 7.38
2-CH_3- 5-Cl-	40	ethanol	111 -111.5	76.47 76.31	6.69 6.48	7.43 7.37

TABLE 1 (continued)

R	Percent Yield	Recrystallizing Solvent	Melting Point	Analyses % C Calcd. Found	 % H Calcd. Found	 % N Calcd. Found
2-Cl- 5-CH_3-	Quant.	ethanol	101.5-102	76.47 76.54	6.69 6.79	7.43 7.46
3-Cl- 4-CH_3-	25	ethanol	111.5-112	76.47 76.23	6.69 6.47	7.43 7.23

Reactions of 1-Aryl-4-(2-hydroxy-3-methoxypropyl)piperazine with Halogenated Compounds

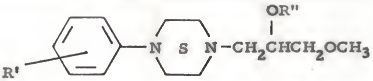
The sodium salt of 1-phenyl-4-(2-hydroxy-3-methoxypropyl)-piperazine was reacted with a variety of halogenated compounds, including seven chloroformates, six alkyl halides and benzoyl chloride. The members of a single series were prepared by the same general procedure and these are explained below. In addition, four new 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazines were prepared by the same procedure as was used for the preparation of 1-phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine described on page 10. Each of these was reacted with methyl iodide to give the corresponding methyl ether. In the case of 1-(2-methoxy)phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine, one preparation using two equimolar amounts of methyl iodide gave not only the ether derivative of the hydroxyl group but produced alkylation of one of the piperazine nitrogens as well, yielding the quaternary ammonium iodide. Table 2 lists the physical and analytical data for the products.

Reaction with chloroformates

1-Phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine (0.12M) and sodium (0.1M) were placed with toluene (200 ml.) in a 500 ml.,

TABLE 2

DERIVATIVES OF 1-ARYL-4-(2-HYDROXYPROPYL)PIPERAZINES



$-CH_2CH(OR'')CH_2OCH_3$

R'	R"	Percent Yield	Recrystal-lizing Solvent	Boiling or Melting Point	Analyses % C Calcd. Found	% H Calcd. Found	% N Calcd. Found	Neut. Equiv. Calcd. Found
H	$-\overset{\overset{O}{\parallel}}{C}O\text{-}CH_3$	25	abs. ethanol-dry acetone	176 -176.5 (d)	55.73 56.03	7.31 7.26	8.13 8.28	345 343
H	$-\overset{\overset{O}{\parallel}}{C}O\text{-}C_2H_5$	29	n-butanol	162 -163 (d)	56.40 57.08	7.58 7.68	7.81 7.94	359 359
H	$-\overset{\overset{O}{\parallel}}{C}O\text{-}n\text{-}C_3H_7$	56	ethanol-ether	161 -162 (d)	57.98 58.02	7.84 7.45	7.51 7.88	373 370

TABLE 2 (continued)

R'	R"	Percent Yield	Recrystal-lizing Solvent	Boiling or Melting Point	Analyses % C Calcd. Found	% H Calcd. Found	% N Calcd. Found	Neut. Equiv. Calcd. Found
H	$-\overset{O}{\overset{\|}{C}}O\text{-n-}C_4H_9$	19	water	155.5-156.5	58.98 58.92	8.08 8.13	7.24 7.40	387 386
H	$-\overset{O}{\overset{\|}{C}}O\text{-i-}C_4H_9$	7	benzene	155.5-156.5 (d)	58.98 58.87	8.08 7.89	7.24 7.36	387 386
H	$-\overset{O}{\overset{\|}{C}}O\text{-n-}C_5H_{11}$	20	water	159 -160	59.91 60.09	8.30 8.45	6.99 6.79	401 404
H	$-\overset{O}{\overset{\|}{C}}O\text{-n-}C_6H_{13}$	24	water	155 -156	60.78 61.09	8.50 8.65	6.75 6.68	415 417
H	$-CH_3$	45		135 0.2 mm.	68.15 68.47	9.15 9.54	10.60 10.01	
H	$-C_2H_5$	23		132 0.2 mm.	69.03 69.04	9.41 9.23	10.06 10.26	

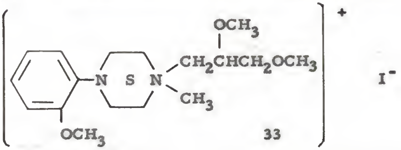
TABLE 2 (continued)

R'	R"	Percent Yield	Recrystallizing Solvent	Boiling or Melting Point	Analyses % C Calcd. Found	% H Calcd. Found	% N Calcd. Found	Neut. Equiv. Calcd. Found
H	$-n-C_3H_7$	29		150 0.2 mm.	69.82 69.75	9.65 9.47	9.58 9.66	
H	$-n-C_4H_9$	14		140 0.1 mm.	70.55 71.04	9.87 10.11	9.14 9.28	
H	$-i-C_4H_9$	8		145 0.2 mm.	70.55 70.14	9.87 9.89	9.14 10.03	
H	$-CH_2\phi$	50		194 -208 0.1 mm.	74.08 74.31	8.29 8.34	8.23 7.94	
$2-CH_3O-$	H	69	ether	81 - 83	64.26 63.98	8.63 8.70	9.99 10.07	
$2-C_2H_5O-$	H	40	benzene	71 - 71.5	65.27 66.32	8.90 8.80	9.52 9.74	
$4-C_2H_5O-$	H	57	benzene	96 - 97	65.27 66.45	8.90 8.88	9.52 9.65	

TABLE 2 (continued)

					Analyses			
R'	R"	Percent Yield	Recrystallizing Solvent	Boiling or Melting Point	% C Calcd. Found	% H Calcd. Found	% N Calcd. Found	Neut. Equiv. Calcd. Found
2-n-C_3H_7S-	H	59		177 0.2 mm.	62.93 62.92	8.70 8.89	8.63 8.77	
2-CH_3O-	-CH_3	33		147 0.3 mm.	65.28 65.67	8.90 8.92	9.52 9.42	
2-C_2H_5O-	-CH_3	18		147 0.3 mm.	66.20 65.93	9.15 8.98	9.09 9.05	
4-C_2H_5O-	-CH_3	46	(distilled)	41 - 43	66.20 66.11	9.15 9.10	9.09 9.05	
2-C_2H_5S-	-CH_3	15		173 -180 0.3 mm.	63.86 63.97	8.93 8.85	8.28 8.55	
H	$-\underset{\underset{O}{\|}}{C}\phi$	70	ether	104.5-105	71.16 70.91	7.39 7.48	7.91 7.83	

TABLE 2 (continued)

R'	R"	Percent Yield	Recrystal-lizing Solvent	Boiling or Melting Point	Analyses % C Calcd. Found	 % H Calcd. Found	 % N Calcd. Found	Neut. Equiv. Calcd. Found
		33		164 -164.5	46.79 46.66	6.70 6.72	6.42 6.21	29.09[a] 29.27

a. Iodine analysis

3-neck, round-bottom flask equipped with a condenser and outlet tube which led to a rotary wet-test meter for measuring hydrogen evolution. The contents were refluxed until the calculated amount of hydrogen had evolved. The solution was cooled and, if any unreacted sodium still remained, it was either removed or the solution of the alcoholate carefully decanted. The appropriate chloroformate (0.2M) was then added, with stirring, at such a rate as to prevent the temperature rising above 75°. The liquid-solid mixture was stirred for several hours. The solid was then separated by filtration. In some instances the efficiency of the separation was improved by dissolving the crude solid in aqueous sodium carbonate and extracting the resulting solution once or twice with ether. The toluene-ether solution of the carbonic acid ester was then concentrated to approximately 100 ml. on a rotary evaporator and the product was precipitated as the monohydrochloride with anhydrous hydrogen chloride. The crude material was recrystallized until a product with the proper neutral equivalent was obtained.

Reaction with alkyl halides

The preparation of the sodium alcoholate with metallic sodium was the same as that described above. In the alternative procedure involving the use of sodium hydride, the hydride (0.1M) was placed in the reaction vessel with the toluene (or benzene) and

1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine in a solution of the same solvent was added dropwise through a pressure-equalizing addition funnel. The reaction was considered complete when the calculated amount of hydrogen had evolved. The solution was cooled and the desired alkyl halide was added dropwise with stirring. When it appeared that no more solid was precipitating, the stirring was stopped and the reaction mixture poured into about an equal volume of water. The resulting oil layer was separated and the aqueous layer was extracted with benzene, ether or heptane. Upon evaporation of the solvents in a rotary evaporator, a solid sometimes appeared which was removed by filtration and determined to be the starting alcohol, 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine. A small amount of sodium was added to the liquid product containing the desired ether in a distillation flask and the contents heated at a temperature sufficient to melt the sodium for an hour or so under vacuum. The temperature was then raised and the 1-aryl-4-(2-alkoxy-3-methoxypropyl)piperazine was distilled.

When twice the equimolar amount of methyl iodide was added to the sodium salt of 1-(2-methoxy)phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine voluminous precipitation occurred. The precipitate was removed by filtration and partially dissolved in aqueous sodium hydroxide. The undissolved portion was again removed by filtration and recrystallized from a methanol-ethyl acetate solution. Elemental analysis indicated this to be the quaternary ammonium iodide.

Reaction with benzoyl chloride

Sodium hydride was reacted with 1-phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine as described above except that the solvent used was dimethyl formamide at 60° to 70°. Benzoyl chloride was added dropwise with stirring. The solution was then cooled and a flocculent precipitate began to separate at approximately 40°. The mixture was stirred at room temperature for twenty-four hours and filtered. The product was recrystallized from a dimethyl formamide-water solution, again from ethanol, and finally from ether.

Synthesis of Benzhydryl Ethers of 1-Aryl-4-(2-hydroxy-3-methoxypropyl)piperazine

The synthesis of the benzhydryl ethers of the 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazines was accomplished by the preparation of 1-halo-2-benzhydryloxy-3-methoxypropane and reaction of this intermediate with the appropriate N-substituted piperazine. Two such ethers have been prepared. The 1-halo-2-benzhydryloxy-3-methoxypropane was prepared by the reaction of benzhydryl halide with 1,2-epoxy-3-methoxypropane.

The preparation of 1-bromo-2-benzhydryloxy-3-methoxypropane in heptane solution is described below. It was also prepared in 60 percent yield in the same manner (except that the reaction time was cut to three and one-half hours) as that described for the preparation of 1-chloro-2-benzhydryloxy-3-methoxypropane.

1-Bromo-2-benzhydryloxy-3-methoxypropane

A stirred solution of benzhydryl bromide (0.1M) in heptane (100 ml.) was warmed to 75° to 80° and 1,2-epoxy-3-methoxypropane (0.11M) was added dropwise through an addition funnel. After complete addition, the solution was refluxed for one and one-half hours. The solvent and lower boiling components were removed by distillation at atmospheric pressure and the residue distilled to give 48 percent yield of product, b.p. 147-150°, 0.1 to 0.2 mm. The analysis calculated for $C_{17}H_{19}BrO_2$: C, 60.90; H, 5.71; Br, 23.84. Found: C, 60.88; H, 5.92; Br, 23.82.

1-Chloro-2-benzhydryloxy-3-methoxypropane

1,2-Epoxy-3-methoxypropane (0.68M) and redistilled benzhydryl chloride (0.33M; b.p. 97°, 0.2 mm.) were put in a 300 ml., 3-neck, round-bottom flask equipped with an inlet tube, thermometer, condenser, and outlet tube. The system was flushed with nitrogen, a bubble-counter attached to the outlet tube, and the flow rate adjusted to maintain a slight positive pressure. When the temperature had been raised to approximately 90°, water (about 0.5 ml.) was added. The mixture was stirred under nitrogen at a temperature of 115° to 125° for 4 days. The product was cooled under nitrogen at a slightly increased flow rate. The excess epoxide was partially removed by distillation at atmospheric pressure. The residue was distilled bulb-to-bulb to give 78 percent yield of crude 1-chloro-2-benzhydryloxy-3-methoxypropane, b.p. 138-144°, 0.2 mm. On cooling to room temperature, the distillation residue (14%) partially solidified. The addition of methanol facilitated crystallization and subsequent filtration. The melting point and nuclear magnetic resonance spectrum indicated that the product thus obtained was dibenzhydryl ether. The crude 1-chloro-2-benzhydryloxy-3-methoxypropane was redistilled at 125-126°, 0.1 mm., through a 6-inch Vigreaux column. The analysis of the product calculated for $C_{17}H_{19}ClO_2$: C, 70.21; H, 6.59; Cl, 12.19. Found: C, 70.47; H, 6.77; Cl, 12.06.

Preparation of 1-aryl-4-(2-benzhydryloxy-3-methoxypropyl)piperazines

N-Phenylpiperazine (0.1M) and sodium carbonate (0.1M) were heated with stirring for about half an hour at 100° to 135°. The mixture was cooled and 1-chloro-2-benzhydryloxy-3-methoxypropane (0.1M) was added dropwise. The mixture was then heated at 115-125° with stirring for several hours. The solids were removed by filtration, dissolved in aqueous alkali and extracted with ether. The dried ether layer was combined with the filtrate and evaporated on the steam bath. The residue failed to crystallize on cooling. Additional N-phenylpiperazine (0.1M) was added and the mixture was heated on the steam bath. Needles began to form almost immediately. The heating was continued with occasional shaking for about twelve hours. The product was then thoroughly mixed with ether, filtered, and the ether evaporated on the steam bath. The excess phenylpiperazine was removed by distillation under vacuum and the residue was poured into methanol. Ether was added until the product precipitated as crystals rather than an oil when cooled. The yield was 34 percent and upon recrystallization from a methanol-ether solution, the product melted 63.5-65°. The analysis calculated for $C_{27}H_{32}N_2O_2$: C, 77.84; H, 7.74; N, 6.73. Found: C, 77.77; H, 7.73; N, 6.53. The monohydrochloride melted 141°. Neutral equivalent: calculated, 453; found, 458.

1-p-Chlorophenyl-4-(2-benzhydryloxy-3-methoxypropyl)-piperazine was similarly prepared from N-p-chlorophenylpiperazine and 1-bromo-2-benzhydryloxy-3-methoxypropane. The yield was

70 percent and when recrystallized from a methanol-ether solution the product melted 89-89.5°. The analysis calculated for $C_{27}H_{31}ClN_2O_2$: C, 71.90; H, 6.93; N, 6.21. Found: C, 72.94; H, 7.00; N, 6.04.

Reactions for Proof of Structure of Benzhydryl Ether Derivatives

Ether cleavage of 1-phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine with hydrobromic acid

1-Phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine (0.008M) was dissolved in 40 percent aqueous hydrobromic acid (50 ml.) and heated to boiling. Solid sodium hydroxide was added until the solution was basic. The solution was extracted with ether and the extract was dried and evaporated on the steam bath. A solid product was obtained and recrystallized from benzene-heptane solution. M.p. 106.5-107.5°. If the product is assumed to be 1-phenyl-4-(2,3-dihydroxypropyl)piperazine, the yield was 53 percent.

Ether cleavage of 1-phenyl-4-(2-benzhydryloxy-3-methoxypropyl)piperazine with hydrobromic acid

1-Phenyl-4-(2-benzhydryloxy-3-methoxypropyl)piperazine (0.005M) was treated with 40 percent aqueous hydrobromic acid (50 ml.) using the same procedure described immediately above. Assuming the product also to be the same, the yield was 27 percent. M.p. 106.5-107.5°.

Reaction of 1-phenyl-4-(2-hydroxy-3-chloropropyl)piperazine with aqueous sodium hydroxide

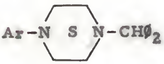
An unweighed amount of 1-phenyl-4-(2-hydroxy-3-chloropropyl)piperazine was refluxed several hours in 25 percent aqueous sodium hydroxide. The oil layer was removed, dissolved in benzene, and extracted several times with water. The water extracts were combined and extracted once with benzene. The benzene solution was dried and the benzene removed by evaporation on the steam bath. The residue crystallized upon cooling. The crude product melted 103-105°.

A mixture of the products obtained from the above three reactions failed to show a depression in melting point. The infrared spectrum of the product was consistent with its identification as 1-phenyl-4-(2,3-dihydroxypropyl)piperazine.

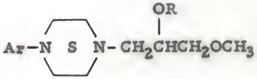
CHAPTER III

GENERAL DISCUSSION

As already mentioned, the compounds prepared in this research correspond to two general formulas:



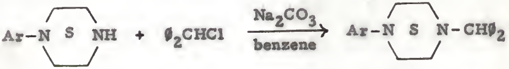
I



II

$$R = \text{CO-alkyl},\ \overset{O}{\overset{\|}{C}}\phi,\ \text{alkyl, benzyl, benzhydryl}$$

The benzhydryl piperazines, represented by formula I, were obtained as reaction products of benzhydryl chloride with substituted piperazines.



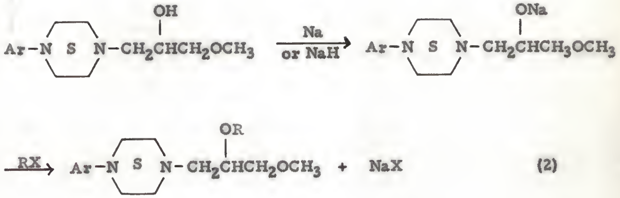
(1)

Although the products reported were prepared in refluxing benzene solution in the presence of sodium carbonate, it was also found that the benzhydryl piperazine hydrochlorides can be prepared by simply heating the aryl piperazine and the benzhydrylchloride on the steam bath for an hour or so. This method, of course, precludes the presence in the molecule of a group, such as an alkoxy group, which would not remain intact in the presence of hydrogen chloride at this temperature. The free amine was recovered by treatment of the hydrochloride with aqueous alkali and extraction with ether.

Even these conditions are not as severe as those employed by Kyrides[30] who prepared similar compounds by heating benzhydryl bromide and substituted piperazine with triethylamine in toluene solution at 150° for seven hours.

The fact that all of the yields from the preparation of the benzhydryl piperazines are less than 41 percent should not be interpreted as an indication of the difficulty of reaction. The evaporation of the solvent extract of the reaction mixture on the steam bath frequently gave an acid residue. This was indicative of a reaction of residual starting materials in the extract and it seems almost certain that an increase in reaction time would have resulted in an increased yield.

Except for the benzhydryl derivatives, compounds of the type represented by formula II were prepared by reaction of the appropriate halide with the sodium salt of 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine.



(2)

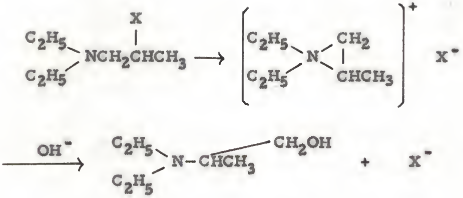
Both sodium hydride and metallic sodium were used for the preparation of the sodium salt, but in many cases it proved difficult, because of the proximity of the respective boiling points, to separate the final reaction product from the oil in which the sodium hydride was suspended. Consequently, with few exceptions, the compounds reported here were prepared using metallic sodium. Furthermore, the sodium alcoholate, which was soluble in the benzene or toluene in which it was prepared, could be decanted from any unreacted sodium before addition of the halide to the solution.

Invariably, the crude product was contaminated with at least a small amount of the starting alcohol. Purification processes were repeated in each case until the infrared spectrum of the product showed little or no absorption below 3.0 microns. The benzoate derivative, which is a solid, was purified by recrystallization. The benzyl ether and alkyl ether derivatives were obtained as liquids. The benzyl ether was purified by the second distillation under vacuum.

However, each of the alkyl ethers distilled simultaneously with the respective alcohol from which it had been prepared. An attempt to separate the ether from the crude mixture by esterification of the unreacted alcohol with phthalic anhydride resulted in an incomplete reaction. The product was obtained pure by distillation under vacuum from sodium.

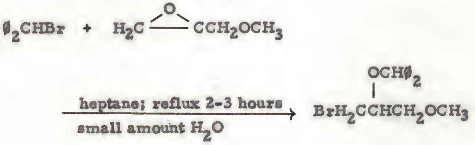
In the special case of the carbonic acid esters, the products were precipitated from solution as the amine monohydrochlorides. The hydrochlorides were recrystallized from the designated solvent until the melting-point ranges and infrared spectra indicated that they were pure. Since these compounds are to be tested in the form of their hydrochlorides for biological activity, the free amines were not recovered.

Attempts to prepare the benzhydryl ethers from the sodium salt of 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine were unsuccessful. Alternatively, benzhydryl ethers may be prepared by the reaction of benzhydrol or its sodium salt with the appropriate chloride.[31] However, it has been shown that, in the preparation and reaction of β-halamines of this type, rearrangements through an intermediate ethyleneimmonium ion occurs:[32]

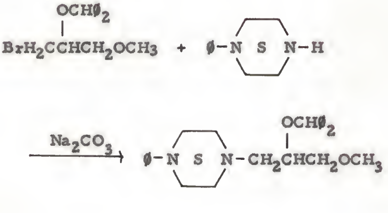


(3)

Therefore, another synthetic route was required. Investigation of various possibilities resulted in the discovery that the reaction of the benzhydryl halide with 1,2-epoxy-3-methoxypropane yields the desired benzhydryl ether.

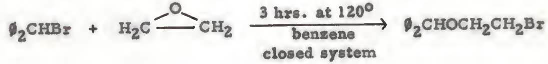


(4)



(5)

It should be recognized that alkyl halides do not generally react with epoxides. Benzhydryl bromide has been known to react with ethylene oxide under forcing conditions.[33]



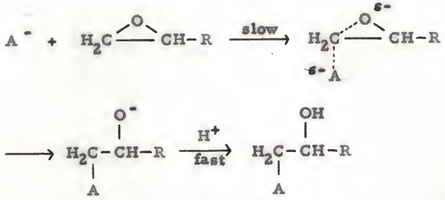
$$\phi_2CHBr + H_2C\overset{O}{\longrightarrow}CH_2 \xrightarrow[\text{benzene}\\ \text{closed system}]{\text{3 hrs. at }120^\circ} \phi_2CHOCH_2CH_2Br \quad (6)$$

Equation (4) above, however, represents the first reported reaction of an alkyl halide with a substituted epoxide. It is novel in that its only counterpart is the addition of methyl iodide, ethyl iodide, ethyl bromide and n-propyl bromide to cyclohexene epoxide, and these reactions were also carried out under forcing conditions in sealed tubes.[34] The reaction of equation (4) has been accomplished under the relatively mild conditions of moderate temperature and atmospheric pressure. Furthermore, the less reactive and relatively inexpensive benzhydryl chloride can also be made to undergo addition to 1,2-epoxy-3-methoxypropane with excellent yields of the desired ether. In fact, the chloride is in some respects the more desirable halogen intermediate since in the preparation of derivatives such as the benzhydryl ethers described here, the production of hydrogen chloride instead of hydrogen bromide as a by-product potentially has less tendency to enter into side reactions with the product molecule.

It was not the purpose of the present work to establish the mechanism for the benzhydryl halide-epoxide reaction and without further experimental evidence it would be impossible to do this. However, in the light of other work which has been done on the mechanism of epoxide ring openings and in view of the fact that the major products of the present halide-epoxide reactions are known, a discussion of the probable mechanism would seem to be in order.

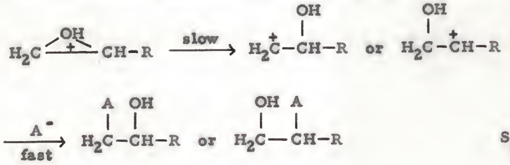
Generally speaking, three factors are usually considered in the investigation of the orientation of such ring openings: (1) either the pH or the polarity of the reacting medium, (2) the substituents attached to the carbon atoms of the epoxide ring and (3) the mechanism by which the addition to the ring occurs. The three factors are apparently interdependent and can hardly be considered separately in arriving at a satisfactory explanation for results of certain addition reactions to epoxides.

Perhaps the most common type of addition under basic conditions is the bimolecular, S_N2 type in which a nucleophilic reagent displaces the epoxide oxygen from one of the carbons to which it is attached.



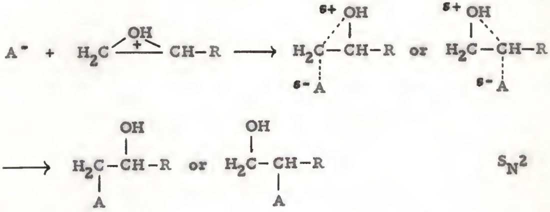
S_N2

In acidic media, the addition may take either or both of two different routes. The first is the S_N1, or unimolecular, addition in which there is a preliminary protonation of the epoxide oxygen followed by the slow, or rate-determining, step which is the rupture of the carbon-oxygen bond before the addition of the nucleophile.



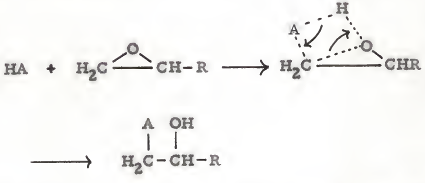
S_N1

The second is a modified S_N2 type in which the nucleophile attacks one of the positive sites (carbons) of the protonated epoxide ring.



S_N2

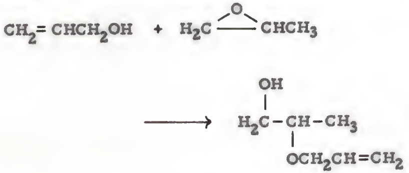
A third mechanism, which is rarely considered in epoxide openings, is the so-called "four-centered" reaction.



This particular mechanism was proposed by Brewster[35] to explain the retention of configuration in certain reactions involving nucleophilic attack at substituted carbon atoms of the epoxide ring.

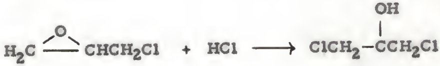
It should be apparent from observation of the factors involved in the equilibrium between reactants and the proposed transition state in each of the above examples of acid-catalyzed mechanisms that a decrease in the polarity of the solvent should not necessarily affect the rate at which the transition state is formed by the S_N1 mechanism. However, in the S_N2 reaction in which two separately charged particles have combined to form one particle through which the charges have been dispersed, a decrease in polarity of the solvent would be expected to increase the rate at which the transition state is formed which in turn provides an increase in the rate of formation of S_N2 reaction products.

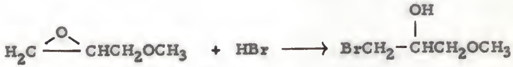
The influence of R in the examples above has been shown to affect the orientation of the ring opening. If R is an electron-donating group, then in both the S_N1 and the S_N2 mechanism, the development of positive or partial positive charge on the adjacent carbon will occur more readily than on the terminal carbon atom. This results from the dispersion of the positive charge over the R-group as a result of its electron donor behavior. Since the breaking of the carbon-oxygen bonds of the ring involves a transfer of electrons from the carbon to the oxygen, the net result of the electron-donating effect of R is to facilitate the release of electrons by the secondary carbon and cause the carbon-oxygen bond to this carbon to be the weaker of the two. Consequently, this particular bond is more subject to bond-breaking and a preponderance of the nucleophilic additions would be expected at the secondary carbon. This effect is illustrated by the formation of the secondary ether (along with a lesser amount of primary ether) in the acid catalyzed reaction between propylene oxide and allyl alcohol.[36]



(mostly)

Conversely, an electron-withdrawing group would tend to inhibit the development of positive charge on the adjacent carbon atom and promote nucleophilic addition at the primary carbon. This is indeed the case in the addition of halogen acids to epoxides substituted with electron-withdrawing groups as $-CH_2Cl$[37] and $-CH_2OCH_3$.[38]



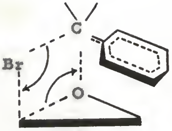


Preliminary preparations using a variety of solvents indicated that a higher yield of 1-bromo-2-benzhydryloxy-3-methoxypropane is obtained from reactions in heptane than in either of the more polar solvents, dry acetone or the dimethyl ether of diethylene glycol. This, of course, is consistent with reaction by the acid-catalyzed S_N2 mechanism in which the charge carried by the reacting particles has been spread over the combination of the particles in the transition state.

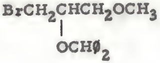
It was found, however, that the formation of the desired product was facilitated by the addition of a small amount of water. Whether this is needed for solvolysis of the benzhydryl halide or for preliminary protonation of the epoxide was not determined.

Although the rate of the "four-centered" reaction is not ordinarily subject to influences from change of solvents, the following points may be made in consideration of this mechanism.

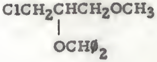
First of all, this particular path of reaction would not require the ionization of the benzhydryl halide. This is consistent with the fact that it can be run in heptane, although as mentioned above the rate is much slower in the absence of water. Secondly, the structure of the transition state would allow the conjugation of the benzhydryl group with the epoxide ring and provide the driving force for the reaction.



The orientation of the ring opening of the epoxide ring in 1,2-epoxy-3-methoxypropane is the same for reaction with benzhydryl chloride as for benzhydryl bromide. This is verified by the preparation of identical 1-phenylpiperazine derivatives from the intermediates obtained from the two benzhydryl halide-epoxide reactions. Presumably, from the comparison with the addition of hydrogen bromide, these intermediates have the formulas

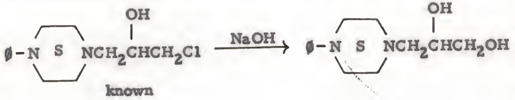

$BrCH_2\underset{\underset{OCH\phi_2}{|}}{CH}CH_2OCH_3$

and

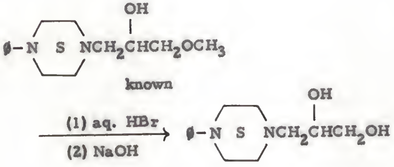

$ClCH_2\underset{\underset{OCH\phi_2}{|}}{CH}CH_2OCH_3$

The benzhydryl ether from the reaction of benzhydryl halide with the sodium salt of 1-phenyl-4-(2-hydroxy-3-methoxypropyl)piperazine was not prepared and isolated in the pure state. Consequently, the structure of the halo-intermediates could not be established by the product of their reactions with 1-phenylpiperazine.

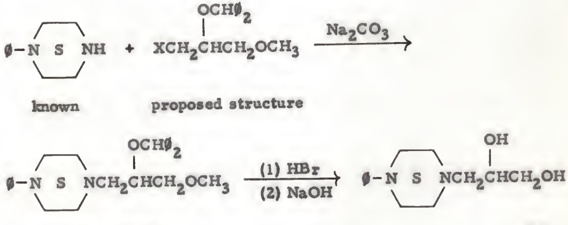
For this reason, the following series of reactions has been effected to give substantial proof of their respective structures.



(7)



(8)



(9)

The same solid product (m.p. 106.5-107.5°) was obtained from all three reactions. The structure indicated as product in the above reactions is the only product which would be expected from reaction (7). Since the products from (7) and (8) were the same, then it must be concluded that no rearrangement occurred in reaction (8) by the formation of a secondary bromide intermediate and subsequently of an ethyleneimmonium ion as described in reaction (3). Since no such rearrangement occurred in reaction (8), then it appears improbable that it would occur in reaction (9). Therefore, the proposed structure for the piperazine product in reaction (9) must be correct. It then follows that since no rearrangement occurs in the displacement of halogen by 1-phenylpiperazine[28] that the identification of the halo-intermediates as 1-halo-2-benzhydryloxy-3-methoxypropane is also correct.

Qualitative observations of changes in the infrared spectrum of the product which was shown to be 1-halo-2-benzhydryloxy-3-methoxypropane have indicated that this material upon prolonged standing in air in a screw-cap bottle probably forms a hydroperoxide. Unless stored under an inert atmosphere, the reagent becomes contaminated with decomposition products of the hydroperoxide.

CHAPTER IV

SUMMARY

Eleven new 1-aryl-4-benzhydryl piperazines have been prepared by the reaction of benzhydryl chloride with arylpiperazines. The aryl substituents of piperazine were various methyl-, chloro-, and methoxy-substituted phenyl groups.

The sodium salt of 1-phenyl-4-(2-hydroxy-3-methoxypropyl)-piperazine was reacted with halogenated compounds, including seven chloroformates, six alkyl halides and benzoyl chloride, to give the corresponding 1-phenyl-4-propylpiperazine derivatives. In addition, four new 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazines were prepared and their sodium salts reacted with methyl iodide to give the methoxy derivatives. An excess of methyl iodide was reacted with one of the latter ethers to give the quaternary ammonium iodide.

Both 1-chloro-2-benzhydryloxy-3-methoxypropane and 1-bromo-2-benzhydryloxy-3-methoxypropane were prepared. These compounds are also new and were used to prepare two new 1-aryl-4-(2-benzhydryloxy-3-methoxypropyl)piperazines.

The difficulty in the preparation of benzhydryl ethers of 1-aryl-4-(2-hydroxy-3-methoxypropyl)piperazine from its sodium salt resulted in the discovery that benzhydryl bromide and benzhydryl chloride react with substituted epoxides to give benzhydryloxy-halide derivatives of the epoxide. This reaction was accomplished under conditions of moderate temperature and atmospheric pressure whereas on the two occasions in which previous authors have effected the addition of alkyl halides to epoxides it was done by reactions in sealed tubes at relatively high temperature. The addition of alkyl chlorides to epoxides is unreported and the discovery of the above reaction should allow the synthesis of benzhydryloxy compounds which heretofore have been economically unfeasible because of low yields and the lack of availability of more reactive starting materials.

Future research in this area of additions to epoxides should be extended to include the establishment of the mechanism whereby the addition is accomplished. The preponderance of evidence at present indicates that the route is probably S_N2 but the "four-centered" addition cannot be excluded. It should be possible to distinguish between the two by a study of solvent and salt effects on the reaction. The investigation, too, should include the stereochemistry of the addition and additions to more highly substituted epoxides than 1,2-epoxy-3-methoxypropane. The question also arises as to whether the epoxide ring could be opened under mild conditions with other halides such as allyl halides, alkyl iodides, or such halogen compounds as isopropyl halide whose ethers are difficult to prepare. The benzhydryloxy ether is suspected of forming a hydroperoxide on prolonged standing, but its identity and that of its decomposition products are unverified.

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